



GB993125

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Desc

Claims

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**Novel pharmac utical compositions for the tr atment of fatigu**

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Inventor(s):
Applicant(s): CFMC
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Abstract

Pharmaceutical compositions for the treatment of fatigue comprise phosphocreatine or phosphocreatinine e.g. as their disodium salts or their acid addition salts with an amino alcohol, and a solid diluent or carrier. Non-toxic salts of succinic acid and potassium may also be present. They may be in orally administrable forms, e.g. cachets.

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PATENT SPECIFICATION

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NO DRAWINGS.

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SPECIFICATION NO. 993,125

By a direction given under Section 17 (1) of the Patents Act 1949 this application proceeded in the name of ETABLISSEMENTS KUHLMANN, a French body corporate, of 25 Boulevard de l'Amiral Bruix, Paris 16^{eme}, France.

THE PATENT OFFICE

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- 5 declare the invention, for which we pray
that a patent may be granted to us, and the
method by which it is to be performed, to be
particularly described in and by the follow-
ing statement:—
- 10 The present invention concerns novel
pharmaceutical compositions for the treat-
ment of fatigue.
- 15 The importance of phosphocreatine or phos-
phagen in the course of muscular contrac-
tion, and particularly of cardiac action, is well
known. In man this phosphagen constitutes
a form of reserve energy, owing to the link-
age rich in energy which its molecule con-
tains. This energy is rapidly and easily utilis-
able for numerous metabolic reactions, such
as muscular contraction, or for numerous
synthesis reactions through the rephosphory-
lating of the adenosine diphosphate with
phosphorylated groups. However, phospho-
creatine has not been proposed until now as
a substance for the treatment of fatigue.
- 25 Now, it has been found that, with admini-
stration either as salts of phosphocreatine
or as salts of phosphocreatinine, it is
possible to combat fatigue with great
efficacy; by varying the posology, the source
of energy which it requires to reconstitute
its metabolic reserves can be placed at the
disposal of the organism.
- 35 According to the present invention there-
fore pharmaceutical compositions for the
treatment of fatigue are provided containing
a salt of phosphocreatine and/or a salt of
phosphocreatinine with a pharmaceutically
acceptable solid carrier.
- 40 However, fatigue is a syndrome which is
characterised by disturbances affecting the

creatine or of phosphocreatinine with pro-
ducts acting at the nervous level and/or
with products acting at the general meta-
bolism level.

As a product acting against nervous
fatigue the succinate of dimethylcolamine,
methylcolamine or colamine may be used.
Potassium succinate can be used as a pro-
duct acting at the level of general meta-
bolism.

At the level of general metabolism, the
succinic ion (in the form, for example, of
potassium succinate or the succinate of
methylcolamine) plays an important part in
reducing fatigue. Its important metabolic
turnover makes it an excellent source of
metabolites; it is in fact a very important
component of the Krebs cycle. This series of
reactions represents the essential source of
energy used by the organism for all the
endergonic processes such as biochemical
syntheses and muscular contraction. It may
therefore be thought—and our pharmaco-
dynamic experiments have demonstrated this
to perfection—that the administration of
succinate, and more particularly potassium
succinate, by encouraging this creation of
energy, has an interesting anti-fatigue action.

The potassium cation for its part is essen-
tial to cell life and plays an important part
in muscular contraction. The state of fatigue
is bound up with disturbances in the
potassium-sodium ionic equilibrium, the de-
contraction being related particularly to the
recharging of the muscular fibre with
potassium. The potassium cation can be
introduced into the anti-fatigue compositions
of the present invention not only in the form

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of potassium succinate but in the form of potassium fumarate.

Methylcolamine (in the form of methylcolamine succinate, for example), the precursor of choline and an integral part of the choline cycle, reduces nervous fatigue.

The preferred salts of phosphocreatine and phosphocreatinine, namely sodium phosphocreatinate and sodium phosphocreatininate, have practically no toxicity, either taken orally or by injection.

Neutral potassium succinate has a slight toxicity (on adult mice, maximum non-toxic dose of 1 gram per kilogram of animal, 50% lethal dose of 2.30 grams per kilogram. The acid succinate of N-methylcolamine has practically no toxicity.

The invention will be more clearly understood by reference to the following examples which are purely illustrative.

EXAMPLE 1.

A powder containing 25.42 grams of sodium phosphocreatinate with four molecules of water of crystallization, 70.62 grams of neutral potassium succinate and 4.96 grams of acid succinate of N-methylcolamine is prepared in a mixer. The mixing is continued with exclusion of moisture until a homogeneous powder is obtained. This powder is divided into cachets, which can be packaged in the dry state, at the rate of 354 milligrams per cachet. The cachets are then conditioned and kept free from moisture.

These cachets has been administered to subjects suffering from various types of fatigue, in particular to subjects suffering from post-infectious asthenia and excellent results have been achieved.

EXAMPLE 2.

A mixture of sodium phosphocreatinate, neutral potassium succinate and acid succinate of N-methylcolamine has been tested on emaciated, fatigued or convalescent people who are unfit for regular work. The posology has been at the beginning of 40 centigrams of sodium phosphocreatinate, 100 centigrams of potassium succinate and 28 milligrams of succinate of N-methylcolamine, per day for 4 days, then a second treatment after a rest of 4 days if a significant result was not obtained at first. The results were mostly sufficiently satisfactory to avoid the necessity of a continuation of the treatment.

In view of the low toxicity of the product, 56 milligrams per day of succinate of N-methylcolamine were administered in the majority of cases instead of 28.

The tolerance to the different doses used was excellent (25 out of 26). There has not been any troublesome therapeutic incidence on the blood count, but on the contrary, in certain cases a slight increase of the erythrocytes and a tendency to restore the leucocytes figure to normal have been observed.

The clinical results were excellent in the same proportions (25 out of 26). The patients stated that they very quickly felt a sensation of well-being, of relief, and disappearance of their fatigue.

With 12 patients the experimenters have been able to verify a very distinct return of weight. In other respects, the medical treatment in certain cases had a favourable action on hepatic flocculation tests, while the arterial pressure was practically unmodified.

The experimenters have thus been able to declare categorically in favour of the good tolerance and the marked anti-fatigue therapeutic properties of the above composition.

WHAT WE CLAIM IS:—

1. A pharmaceutical composition for the treatment of fatigue containing a salt of phosphocreatine and/or a salt of phosphocreatinine together with a pharmaceutically acceptable solid carrier.
2. A pharmaceutical composition as claimed in claim 1 containing potassium fumarate, potassium succinate, colamine succinate, methylcolamine succinate or dimethylcolamine succinate.
3. Pharmaceutical compositions as claimed in claim 1 or 2 in which the salt of phosphocreatine is the sodium salt.
4. Pharmaceutical compositions as claimed in claim 1, 2 or 3 in which the salt of phosphocreatinine is the sodium salt.
5. Pharmaceutical compositions having a therapeutic action against fatigue substantially as herein described with reference to and as illustrated in either of the Examples.

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